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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,508	06/23/2000	Susan Bonner-Weir	10276-029001	9106

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 07/08/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/602,508	Bonner-Weir et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 23, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15, 17-30, 32-43, 45-57, and 61-73* is/are pending in the application.

4a) Of the above, claim(s) *1-13, 27, and 28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14, 15, 17-26, 29, 30, 32-43, 45-57, and 61-73* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of claims

Claims 14, 15, 17-26, 29, 30, 32-43, 45-57, 61-64 as amended and new claims 65-73 [Paper No. 22 filed 4/23/2003] are under examination in the instant office action.

Claims 1-13, 27 and 28 were withdrawn by examiner as drawn to nonelected inventions without traverse [Paper No. 7 filed 8/03/2001]. Claims 16, 31, 44 and 58-60 were canceled by applicants [Paper No. 22 filed 4/23/2003].

Response to Arguments

Applicants' amendments and arguments filed 4/23/2003 [Paper No. 22] have been fully considered but they are not persuasive for the reasons below.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14, 15, 21-26 as amended and new claims 65-67 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Kerr-Conte et al. [IDS-AH, 1995].

Claims are directed to a method for obtaining pancreatic islet cells from dedifferentiated pancreatic cells wherein method comprises the active step of culturing a population of dedifferentiated pancreatic cells in the presence of a component of extracellular matrix (ECM) after addition of ECM, wherein the dedifferentiated pancreatic cells have undergone proliferation, do not express insulin and express markers of dedifferentiated pancreatic cells

including IPF-1, PDX-1, Stf-1, IDX-1 and Pref-1. The culturing step results in obtaining pancreatic islet cells. Some claims are further drawn to the population of dedifferentiated pancreatic cells which express a marker indicative of expansion such as cytokeratin in the method for obtaining islets cells. Some claims are further drawn to the method of producing pancreatic islet cells which form buds or which are hormone positive or express insulin or glucagon.

Kerr-Conte et al. [IDS-AH] disclose an *in vitro* model method for neogenesis of pancreatic islet cells, wherein the method comprises the step of culturing proliferating cysts or islets which contain a population of dedifferentiated pancreatic cells in the presence of a component of extracellular matrix (ECM) such as the Matrigel preparation (col. 2, par. 3, line 5). The culturing step in the method of Kerr-Conte et al. results in obtaining pancreatic islet cells or endocrine cells which express insulin, glucagon and somatostatin (col. 2, lines 5-6).

The starting material in the method of Kerr-Conte et al. such as islets or proliferating cysts are considered to comprise a population of dedifferentiated pancreatic cells as required by the claimed method because the presence of dedifferentiated pancreatic cells is evidenced by staining of cytokeratin which is an expansion marker and by ductal epithelial nature of the cells within the proliferating cysts as disclosed by Kerr-Conte et al. (col. 1, par. 4, lines 4-6). The ductal epithelial cells are not the islet cells and, thus, they do not produce insulin as required by the claimed method. The reference by Kerr-Conte et al. appears to be silent with regard to expression of other markers such as IPF-1, PDX-1, Stf-1, IDX-1 and Pref-1. However, the

markers of the claimed method are various names of the same markers indicative of expansion of the ductal epithelial cells or exocrine cells (specification page 32, par. 2 and specification page 14, par. 2). Thus, the islets or proliferating cysts comprise cells of a ductal nature and inherently express markers indicative of expansion and, therefore, the islets or proliferating cysts are mixed cell populations comprising dedifferentiated pancreatic cells within the meaning of the claims. The method of claim 14 is not limited to the cells which are free from islets as encompassed by the methods of claims 29 or 44, for example. Therefore, the starting material, the active step and the final result in the method of Kerr-Conte are the same as required by the presently claimed one culturing step method.

The presently claimed method is one active step method because steps of adding ECM to cells and culturing the cells in the presence of ECM can not be reasonably separated into two distinct active steps beyond the meaning of contacting mixed cell populations with ECM. With respect to claim 15, the claim does not have any active step and, thus, the pre-history of dedifferentiated cells before the step of adding/culturing does not provide structural differences in order to distinguish between the claimed method for obtaining pancreatic islet cells and the method of Kerr-Conte et al. for obtaining pancreatic islet cells.

Thus, the cited reference Kerr-Conte et al. [IDS-AH] is considered to anticipate the claimed invention because it discloses a method for obtaining pancreatic islet cells comprising identical active steps of contacting identical structural elements (dedifferentiated pancreatic cells and ECM) which would reasonably be expected to result in production of identical product as the

claimed method. The starting material, the adding of ECM and culturing steps of the reference are the same as claimed. Therefore, the results would be the same.

Applicants' main argument is that ECM is added directly to a population of dedifferentiated pancreatic cells (response page 10). However, islets and/or proliferating cysts are mixed cell populations which are undergoing dedifferentiation as taught by Kerr-Conte and, thus, the mixed cell populations of islets and/or proliferating cysts contain populations of dedifferentiated cells. Therefore, ECM is directly added to dedifferentiated cells within the meaning of the claimed invention. Expression of expansion markers is an inherent event in the method of Kerr-Conte et al. in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14, 21-26, 29, 32, 36-42, 45, 47-51 as amended and new claims 65-73 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Gmyr et al. [IDS-AG].

The claims are directed to a method for obtaining pancreatic islet cells wherein the method comprises steps such as the step of obtaining a population of dedifferentiated pancreatic cells and the step of culturing (contacting) the dedifferentiated pancreatic cells with a component of extracellular matrix (ECM). The culturing step results in obtaining pancreatic islet cells. The population of dedifferentiated pancreatic cells is obtained by culturing and/or proliferating ductal

or exocrine cells (claim 29) or by culturing and/or proliferating adult differentiated pancreatic cells substantially free from islet cells (claim 41). The dedifferentiated pancreatic cells proliferate, express no insulin but do express markers of dedifferentiated pancreatic cells including IPF-1, PDX-1, Stf-1, IDX-1 and Pref-1. Some claims are further drawn to forming a the population of dedifferentiated pancreatic cells which express a marker indicative of expansion such as cytokeratin. Some claims are further drawn to forming pancreatic islet cells which form buds or which are hormone positive or express insulin or glucagon.

The reference by Gmyr et al. [IDS-AG] teaches an *in vitro* method drawn to expansion and differentiation of pancreatic exocrine and endocrine tissues. The method of the reference comprises active steps such as the step of obtaining a population of dedifferentiated pancreatic cells having ductal phenotype (method "C", line 13) and the step of culturing (contacting) the dedifferentiated pancreatic cells with a component of extracellular matrix ECM or with 804G matrix (lines 20-21 as related to method "C"). The starting cellular material of the cited method is clearly free from islet cells as required by the presently claimed method. The dedifferentiated pancreatic cells of the cited reference proliferate and express cytokeratin (line 19) which is a marker indicative of expansion and thus, they are reasonably believed to express additional markers indicative of pancreatic expansion including those listed in the claims in the absence of evidence ti the contrary. The dedifferentiated pancreatic cells proliferate and have a ductal epithelial nature; and, thus, they inherently do not express insulin since the lack of insulin expression is an indication of expansion of pancreatic dedifferentiated cells according to the

applicants definitions (specification page 17, line 9-11). Thus, a substantially similar, if not identical, cell population as in the claimed method is brought into contact and cultured in the presence of ECM. Therefore, the result of the cited method, the obtaining of pancreatic islet cells is an intrinsic result in the method "C" as disclosed by Gmyr et al. The same starting cells, cultured in the same manner, can be reasonably expected to produce the same product.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use exocrine cells or pancreatic cells free from islet cells for cell dedifferentiation, proliferation and further differentiation into islet cells (neogenesis of islet cells) as disclosed by Gmyr et al. [IDS-AG] with a reasonable expectation of success as suggested by Gmyr et al. (last two lines). Thus, the claimed method is obvious to those skilled in the art within the meaning of USC 103, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited reference. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the reference by Gmyr et al. [IDS-AG], applicants' main argument is directed to idea that the cited method does not result in the obtaining pancreatic islet cells but it rather suggests experimentation for further differentiation of dedifferentiated cells. However, the similar, if not identical, protocol is disclosed by the cited reference. The protocol as disclosed by Gmyr comprises step of obtaining dedifferentiated cells and step of culturing dedifferentiated cells in the presence of ECM. Thus, it results in the pancreatic islets cells within the meaning the claims. The structural differences in the methods for obtaining islet cells which are intended by

applicants are uncertain as claimed and as argued. Applicants' arguments are not found convincing because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the cited reference.

Claims 14, 15, 17-26, 29, 30, 32-43, 45-57, 61-64 as amended and new claims 66-73 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerr-Conte et al. [IDS-AH, 1995] or Gmyr et al. [IDS-AG] taken with US 5,681,587 [IDS-AB], US 6,077,692 [C], WO 96/40872 [IDS-AD], Carlsson et al. [W], US 4,439,521 [IDS-AC] and Kerr-Conte et al. [IDS-AY, 1997]

Claims 14, 15, 21-26 and 65-67 have been explained above.

Claims 29, 30, 32, 36-42, 45, 47-51 and 68-73 have been explained above.

Claims 18-20, 33-35, 46 and 61-64 are further drawn to the use of extracellular components comprising laminin, basement membrane derived substance or composition prepared from EHS (Engelbert-Holm-Swarm tumor cells), collagen, entactin, nitogen and heparin sulfate proteoglucan.

Claims 52-56 are further drawn to the use of glucose and growth factors such as epidermal growth factor (EGF) or hepatocyte growth factor (HGF) or keratinocyte growth factors in the media for growth and expansion of pancreatic cells.

Claims 30, 43 and 57 are further drawn to the growth of adherent pancreatic cells till 70% confluency.

Both cited references by Kerr-Conte et al. [IDS-AH] and by Gmyr et al. [IDS-AG] teach the use of extracellular matrix (ECM) in the method for obtaining islet cells including ECM such as collagen and Matrigel {Kerr-Conte et al.} or 804G matrix {Gmyr et al.}. Both cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] teach the use of basic DMEM or RPMI culture medium ingredients including glucose {Kerr-Conte et al} and the use of growth factors including EGF and HGF {Gmyr et al} in the media for growth and expansion of various pancreatic cells.

However, the cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] are silent with regard to particular composition or particular components within the extracellular matrix preparations such as Matrigel or 804G matrix in the methods for obtaining islet cells. But the cited patents US 4,829,000 [B] and US 5,681,587 [IDS-AB] are relied upon to demonstrate that Matrigel and 804G matrix which are used in the methods of the references by Kerr-Conte et al. [IDS-AH] or Gmyr et al. [IDS-AG] comprise laminin, basement membrane derived substances prepared from EHS (Engelbert-Holm-Swarm tumor cell), collagen, entactin, nitogen and heparin sulfate proteoglucan which are the ECM components in the presently claimed method. For example: see US 4,829,000 at col. 3, lines 47-54; col.4, lines 4-7, lines 27-30. See US 5,681,587 at col. 2, lines 33-46; col. 4, lines 15-18. The cited patents teach the use of

extracellular matrix material such as Matrigel or 804G matrix for culturing and expanding various populations of animal cells including pancreatic cells and/or islet cells.

The cited reference by Gmyr et al. [IDS-AG] teaches the use of various growth factors in the method for producing islets cells. But it is silent with regard to keratinocyte growth factor. However, the cited patent US 6,077,692 [C] teaches that keratinocyte growth factor induces and promotes growth and expansion of pancreatic cells including ductal epithelial cells.

In addition, the cited references WO 96/40872 [IDS-AD] and Carlsson et al. [W] are relied upon for the disclosure of known markers indicative of pancreatic cell expansion. For example: WO 96/40872 [IDS-AD] teaches expression of IPF-1 marker by the expanded population of pancreatic progenitor cells as a critical event during pancreas development (page 27, lines 5-10). The reference by Carlsson et al. [W] teaches expression of Pref-1 proteins by pancreatic progenitor cells during pancreatic developments and it teaches that the Pref-1 positive cells further develop into insulin producing differentiated cells.

Further, with respect to claims 15, 30, 43 and 57 the cited patent US 4,439,521 [IDS-AC] and reference by Kerr-Conte et al. [IDS-AY, 1997] provide the teaching about growing adherent pancreatic cells till 70% confluency in the method for obtaining islet cells. For example: US 4,439,521 [IDS-AC] teaches that production or regeneration of islets cells occur after adherence and expansion of pancreatic cells till considerable confluency of about 50% or 60-70%, for example: see col. 9, lines 15-23. The patent also teaches a selection of adherent pancreatic cells for further producing islets cells by teaching step of discarding cells which remain unattached

during expansion of ductal cells (col. 5, lines 25-30). And the reference by Kerr-Conte et al. [IDS-AY, 1997] teaches expansion of ductal epithelial cells in monolayer culture or as adherent cultures on plastic of a culture container before the incorporation of extracellular matrix and additional growth factors permitting differentiation of pancreatic cells in the *in vitro* model for islet cell neogenesis.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the presently claimed basic medium ingredients, growth factors and extracellular matrix materials in the method for producing islets cells because these ingredients and materials have been known and successfully used the methods for producing pancreatic cells including islets cells as taught by all cited references. One of skill in the art would have been motivated to use the presently claimed ingredients and materials for the expected benefit of growing pancreatic cells and/or regenerating pancreatic functions. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The expression of markers indicative of pancreatic cell expansion that are claimed are known in the prior art as evidenced by the cited references WO 96/40872 [IDS-AD] and Carlsson et al. [W]. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to characterize the proliferating pancreatic cells in the presently claimed method because these markers have been known and demonstrated as critical in the development of pancreatic cells and in the development of biological functions of

pancreatic cells including hormone production. One of skill in the art would have been motivated to use the presently claimed markers for selection of population of pancreatic cells which are restricted to differentiation towards hormone producing pancreatic islets cells for the expected benefit of producing pancreatic cells including islets cells and/or regenerating pancreatic functions including hormone production. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

With respect to claims 15, 30, 43 and 57 it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to expand the pancreatic cells in adherent monolayer culture before differentiation in the method for producing pancreatic islets as taught and suggested by the cited prior art because expansion in adherent monolayer cultures allows for a considerable increase of pancreatic cells intended and/or restricted to further differentiation towards hormone producing pancreatic islets cells. One of skill in the art would have been motivated to expand the population of pancreatic cells for maximizing numbers of differentiated hormone producing cells for the expected benefit of producing pancreatic cells including islets cells and/or regenerating pancreatic functions including hormone production. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Therefore, the claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Thus, the claims are properly rejected under 35 USC § 103.

With regard to the secondary references applicant's arguments do not clearly point out the patentable novelty and/or unobviousness that the claims present in view of the state of the art disclosed by the cited references. Further, they do not show how the amendments avoid such references. A general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references is not persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

July 2, 2003.

SANDRA E. SAUCIER
PRIMARY EXAMINER